Intrinsically Disordered Proteins II

2428-Pos Board B120
MD Simulations of Intrinsically Disordered Proteins with Replica-Averaged Chemical Shift Restraints
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Molecular dynamics simulations represent a powerful method for exploring the conformational space of folded proteins. However, the success has so far been limited when the method is applied to intrinsically disordered proteins, a situation that can be attributed to force field inaccuracy and sampling inefficiency. To address the issue, we have developed a strategy to combine the chemical shift information with molecular dynamics simulations for characterizing the structural ensembles corresponding to intrinsically disordered proteins. This method is based on the CamShift protocol for calculating the chemical shifts from inter-atomic distances and to calculate forces that minimize the deviations between experimental and calculated chemical shifts. We have used chemical shifts as these NMR parameters are most convenient for the study of intrinsically disordered proteins, since they, at least in principle, contain information about the structure and dynamics of the molecules. To further enhance the sampling efficiency, the method of metadynamics approach with replica exchange is added to the protocol. The capability of the protocol is demonstrated with in the case of the fragment F4 of tau (tauF4 = tau[Ser208-Ser324]).

2429-Pos Board B121
Molecular Dynamics Studies of Tau Monomer and Dimer Conformations
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The microtubule associated protein tau is important in nucleating and maintain microtubule spacing and structure in neuronal axons. Over-phosphorylated tau is implicated in Alzheimer's disease, where it is found in plaques. Tau likely forms dimers as there is only one microtubule binding domain per tau. Because tau in an intrinsically disordered protein, conventional modeling techniques are not sufficient to accurately describe its structure. In order to simulate tau, we therefore must generate many starting structures in order to form a more complete ensemble. We present preliminary molecular dynamics studies for the n-terminal half of the tau monomer and dimer models (residues 1-241) for tau's normal function as a microtubule spacer and adduce the distributions of end-to-end separations. Because normal tau has several phosphorylation sites, we also investigate how varying phosphorylation locations on the n-terminal half of tau affect its structure.
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2430-Pos Board B122
Molecular Mechanism of Interfacial Adsorption of Disordered Cytoplasmic Tail of Immune Receptors to Membrane
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Important immune responses are linked to Src-mediated phosphorylation of cytoplasmic tyrosine-based motifs (ITAMs). However, the mechanism of how receptor ligation translates into ITAM phosphorylation remains elusive. Here, we use molecular dynamic simulations to explore the potential regulatory involvement of lipid membranes and their influence on the structure and behavior of the cytoplasmic portion of the CD3ε chain of the T-cell receptor. It has been hypothesized that the accessibility of ITAM motifs, such as those in the CD3ε cytoplasmic tail, can be blocked by ionic interactions between positively charged amino acids in receptor tails and negatively charged lipid head groups. This interesting hypothesis represents a previously unrecognized mechanism for control of receptor activation. Our simulations support the notion that the net charge of the lipids present in the membrane can affect peptide-membrane interactions. Results are consistent with experimental findings that show increase interfacial absorption in negatively charged lipid bilayer. Our simulations revealed the conformational variability of the disordered tail, which led to an additional focus on quantifying the interaction by free energy calculations, combined with long time-scale simulations using coarse-grained (CG) approaches. These studies will be extended to address how changes in ionic conditions can modulate phosphorylation of ITAM motifs and lead to regulation of activation of the TCR and other ITAM-bearing immunoreceptors.

2431-Pos Board B123
The Effect of Proline CIS Trans Isomerization on P53 MDM2 Binding
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Proline is unique in that it is the only amino acid that adopts both cis and trans conformations in proteins. In spite of the importance of proline isomerization as a molecular switch in proteins, the effect on protein binding has not been thoroughly investigated, especially for intrinsically disordered proteins (IDPs). In this study, a potential of mean force method was used to calculate the absolute binding affinities for the disordered p53 and MDM2 when the proline in p53 is in both cis and trans conformations. To obtain converged affinity results it was necessary to apply conformational, axial, and orientational restraints to the protein internal coordinates. Our results give insight into how isomerization of a proline affects binding of an IDP to a structured protein.

2432-Pos Board B124
Coarse Grain Models Highlight the Importance of Flexible Disordered Linkers as Determinants of the Phase Behavior in Polyvalent Proteins
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Micron-sized, non-membrane bound cellular bodies can form as the result of collective, heterotypic interactions. These bodies form as the result of micron-scale phase separation akin to liquid-liquid demixing, microscale gelation, or a convolution of these processes. Recent efforts have focused on various biophysical aspects of the phase behavior of macromolecules. This interest is catalyzed by the recognized functional importance of various cellular bodies that result from micron-scale phase transitions.
Li et al. have quantified the effects of polyvalent interactions between macromolecules. For the case of binary interactions between a polymer of SH3 domains and a polymer of proline-rich modules (PRMs), valence refers to the numbers of SH3 domains and PRMs within the respective polymers. Within each polymer, flexible linkers connect the interacting units (SH3 domains and PRMs). Here, we probe the effects of linker properties including lengths, flexibility, and asymmetry of properties between the proteins as determinants of the concentration dependence of phase transitions. Our approach utilizes a lattice-based model that belongs to the same universality class as a three-dimensional Ising model.
We find that that the critical concentration for phase transition is inversely correlated with both the lengths and random-coil-like character of intrinsically disordered linkers. Our observations imply the entropic penalty associated with loop closure promotes the growth of a network. We also show, in consistency with published experiments, that asymmetry in linker lengths of the interacting proteins will manifest itself as asymmetries in details of the concentration dependencies within the phase diagrams of two-component systems. Our results provide a physical rationale for selection against compact disordered linkers that connect interacting modules.
1. Li, P. et al., (2012) Nature, 483: 336-340.

2433-Pos Board B125
Computational Characterization of the Disordered Ensembles of Vasopressin and Oxytocin
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Vasopressin and oxytocin are intrinsically disordered cyclic nanopeptides belonging to a family of neurohypophysial hormones. Vasopressin is an antidiuretic, regulating the retention of water and salts in mammals by indirectly promoting the insertion of aquaporin-2 channels into the epithelial cells of kidney nephron collecting ducts. Oxytocin, in contrast, is a neurotransmitter responsible for inducing labor and the subsequent lactation, as well as modulating some social behaviors. Although unique in their functions, these peptides only differ by two residues and both feature a tocin ring formed by the disulfide bridge between 1st and 6th cysteine residues. This structural similarity was experimentally linked to inhibition of activity at vasopressin receptors by the present oxytocin. Conversely, previous studies have also shown that single-residue mutations in both peptides have a significant impact on their receptor specificities.
In this study we perform molecular dynamics (MD) simulations of wild type and mutant oxytocin and vasopressin in order to characterize their structural